

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
7 December 2000 (07.12.2000)

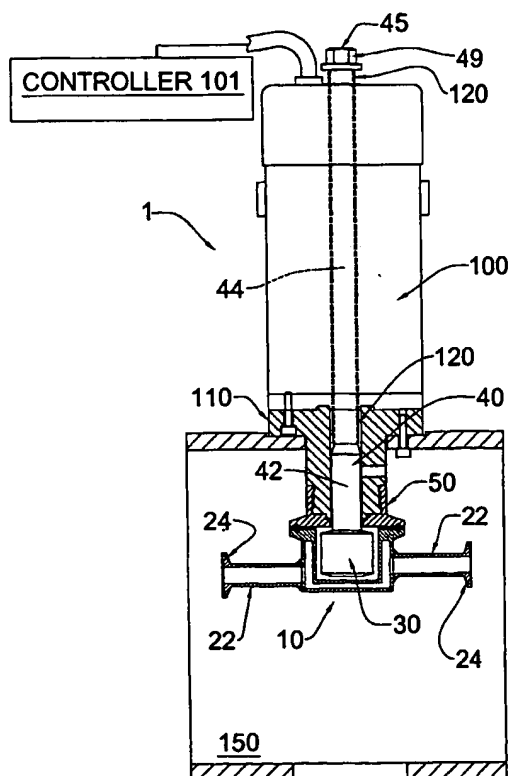
PCT

(10) International Publication Number
WO 00/72973 A1

- (51) International Patent Classification⁷: **B02C 17/16**, 17/20
- (21) International Application Number: PCT/US00/14705
- (22) International Filing Date: 31 May 2000 (31.05.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/137,142 1 June 1999 (01.06.1999) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/137,142 (CIP)
Filed on 1 June 1999 (01.06.1999)
- (71) Applicant (for all designated States except US):
NANOSYSTEMS/DIVISION OF ELAN PHARMACEUTICAL TECHNOLOGIES [US/US]; 3000 Horizon Drive, King of Prussia, PA 19406 (US).
- (72) Inventors; and
(75) Inventors/Applicants (for US only): REED, Robert, Gary [US/US]; 6030 Long Pond Drive, Birdsboro, PA 19508 (US). CZEKAI, David, Alan [US/US]; 310 Nottingham Drive, Spring City, PA 19475 (US). BOSCH, Henry, William [US/US]; 237 Rodney Circle, Byn Mawr, PA 19010 (US). RYDE, Niels, Peter [US/US]; 54 Lloyd Avenue, Malvern, PA 19355 (US).
- (74) Agents: KIMMS, Lyle, K. et al.; Foley & Lardner, Suite 500, 3000 K Street, NW, Washington, DC 20007-5109 (US).
- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE,

[Continued on next page]

(54) Title: SMALL-SCALE MILL AND METHOD THEREOF



(57) Abstract: A small-scale or micro media-mill and a method of milling materials or products, especially pharmaceutical products, use a dispersion containing attrition milling media and the product to be milled. The milling media can be polymeric, formed of polystyrene or cross-linked polystyrene, having a nominal diameter of no greater than 500 microns. Other sizes include 200 microns and 50 microns and a mixture of these sizes. The mill has a relatively small vessel (10) having an opening, an agitator (30), a coupling (50), and a motor. The agitator (30) can have a rotor (32) and a shaft (40) extending therefrom. The rotor (32) can be cylindrical or have other configurations, and can have tapered end surfaces. The coupling (50) can close the vessel opening (56), or attaching the coupling to the motor can close the opening. The coupling has an opening through which the rotor shaft (40) extends into the motor. A sealing mechanism (70), such as a mechanical or lip seals the shaft while permitting the rotor shaft to rotate. The vessel can contain one or more ports for circulating the dispersion, where milling can be made in batches or recirculated through the milling chamber. The media can be retained in the vessel or recirculated along with the process fluid. The rotor is dimensioned so that its outer periphery is spaced with a small gap from an inner surface of the vessel. The vessel also can have a way of cooling the dispersion.

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ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.

Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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SMALL-SCALE MILL AND METHOD THEREOF

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BACKGROUND

Wet media mills, such as the ones described in U.S. Patent Nos. 5,797,550
10 issued to Woodall, *et al*, and 4,848,676 issued to Stehr, are generally used to mill or
grind relatively large quantities of materials. These rather large media mills are not
generally suitable for grinding small or minute quantities. U.S. Patent No. 5,593,097
issued to Corbin recognizes the need for milling small quantities, as small as 0.25
grams, to a size less than 0.5 micron to about 0.05 micron in terms of average
15 diameter in about 60 minutes.

The media mill described in the Corbin patent comprises a vertically oriented
open top vessel, a vertically extending agitator with pegs, a motor for rotating the
agitator, and a controller for controlling the rotational speed. The vessel is a
cylindrical centrifuge or test tube formed of a glass, plastic, stainless steel, or other
20 suitable material having an inner diameter of between 10 to 20 mm. The media
suitable is described as any non-contaminating, wear resistant material, sized
between about 0.17 mm to 1 mm in diameter.

The particulates to be ground and the grinding media are suspended in a
dispersion and poured into the vessel. The agitator, with the peg end inserted in the
25 vessel, is spun. The Corbin patent also discloses that the pegs should extend to
within between about 1 - 3 mm of the sides of the vessel to provide the milling
desired in the shortest possible time without damaging the materials and producing
excessive heat. To avoid splattering created by vortexing of the material during
mixing, the top peg of the mixer is positioned even with the top of the dispersion.
30 No seal or cover is deemed needed during mixing or agitation if this practice is
followed.

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The Corbin patent also discloses that its micro media can be useful for forming medicinal compounds, food additives, catalysts, pigments, and scents. Medicinal or pharmaceutical compounds can be expensive and require much experimentation, with different sizes and quantities. The Corbin patent discloses
5 that the preferred media for medicinal compounds are zirconium oxide and glass. Moreover, pharmaceutical compounds are often heat sensitive, and thus must be maintained at certain temperatures. In this respect, the Corbin patent discloses using a temperature control bath around the vessel.

In the media mill of the type described in the Corbin patent, even if the vessel
10 is filled to the top peg, however, the rotating agitator in the dispersion creates a vortex, which undesirably draws air into the dispersion and foams the dispersion. Moreover, the open top configuration draws in contamination, making the mill unsuitable for pharmaceutical products. The temperature-controlled bath could spill into the open top container and further contaminate the product.

15 There is a need for a micro or small-scale media mill that avoids these problems. The present invention is believed to meet this need.

SUMMARY

The present invention relates to a small-scale or micro media-mill and a
20 method of milling materials, such as pharmaceutical products. The present small-scale mill, which can be vertically or horizontally oriented, can use a dispersion containing attrition milling media and the product to be milled. The milling media can be polymeric type, such as formed of polystyrene or cross-linked polystyrene having a nominal diameter of no greater than 500 microns. Other sizes include 200
25 microns and 50 microns and a mixture of these sizes.

In one embodiment, the mill has a relatively small vessel having an opening, an agitator, and a coupling, and a rotatable shaft mounted for rotation about a shaft mount. The agitator is dimensioned to be inserted in the vessel through the opening. Specifically, the agitator can have a rotor and a rotor shaft extending from the rotor.
30 The rotor shaft is connected to the rotatable shaft. The rotor is dimensioned to be

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inserted in the vessel with a small gap formed between an outer rotating surface of the rotor and an internal surface of the vessel. The coupling detachably connects the vessel to the shaft mount. The coupling has an opening through which a portion of the agitator, such as the rotor shaft, extends. The shaft mount seals the vessel
5 opening to seal the dispersion in the vessel. A seal can be provided to seal the portion of the agitator or the rotor shaft while permitting the agitator to rotate. The rotatable shaft can be driven by a motor or can be a motor shaft of a motor, preferably a variable speed motor capable of 6000 RPM.

In one embodiment, the coupling can have a threaded portion for detachably
10 mounting to the shaft mount and a flange portion for detachably coupling to the vessel. In another embodiment, the coupling is integrally formed with the vessel and has a threaded portion for detachably mounting to the shaft mount.

The mill can include a cooling system connected to the vessel. In one embodiment, the cooling system can comprise a water jacket. Specifically, the
15 vessel comprises a cylindrical inner vessel and an outer vessel spaced from and surrounding the inner vessel. The inner and outer vessels form a chamber therebetween. The chamber can be vessel shaped or annular. A flange connects the upper ends of the inner and outer vessel. The outer vessel (jacket) has at least first and second passages that communicate with the chamber. The cooling system
20 comprises the outer vessel with the first and second passages, which is adapted to circulate cooling fluid.

In an alternative embodiment, the vessel can comprise an inner cylindrical wall having a bottom and an open top and an outer cylindrical wall spaced from and surrounding the inner vessel. The inner and outer cylindrical walls are connected
25 together so that an annular chamber is formed therebetween. At least the first and second passages are formed at the outer cylindrical wall and communicate with the chamber to pass coolant. The bottom extends radially and covers the bottom end of the outer cylindrical wall. The bottom can have an aperture that allows samples of the dispersion to be withdrawn. A valve can close the aperture. Alternatively, the
30 bottom can have an observation window for observing the dispersion.

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In another embodiment, the vessel can include at least one port through which the dispersion is filled. The vessel includes at least two ports through which the dispersion is circulated. In this respect, the cooling system comprises the ports on the vessel for circulating the dispersion. The vessel can be horizontally oriented.

5 The rotor can be cylindrical, and can have tapered end surfaces. In one embodiment, the rotor is dimensioned so that its outer periphery is spaced no larger than 3 mm away from an inner surface of the vessel, particularly when the dispersion contains attrition media having a nominal size of no larger than 500 microns. The spacing or the gap is preferably no larger than 1 mm, particularly when the
10 dispersion contains attrition media having a nominal size of no larger than 200 microns.

In another embodiment, the cylindrical rotor can have a cavity and a plurality of slots that extend between an inner surface of the cavity and an outer surface of the cylindrical rotor. In another embodiment, the cylindrical rotor can have a plurality
15 of channels extending to an outer surface of the cylindrical rotor. In another embodiment, the cylindrical rotor can have a plurality of passageways extending between the tapered end surfaces of the cylindrical rotor.

One method according to the present invention comprises providing a dispersion containing a non-soluble product to be milled and attrition milling media
20 having a nominal size of no greater than 500 microns; inserting the dispersion into a cylindrical vessel; providing an agitator and a coupling that closes the vessel, the coupling having an opening through which a portion of the agitator extends, the agitator comprising a cylindrical rotor and a shaft extending therefrom, wherein the cylindrical rotor is dimensioned so that an outer periphery is no greater than 3 mm
25 away from an inner surface of the cylindrical wall; inserting an agitator into cylindrical vessel and sealingly closing the coupling, wherein the amount of dispersion inserted into the vessel is so that the dispersion eliminates substantially all of the air in the vessel when the agitator is fully inserted into the vessel; and rotating the agitator for a predetermined period.

30 Another method according to the present invention comprises providing a

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dispersion containing a non-soluble product to be milled and attrition milling media having a nominal size of no greater than 500 microns; providing an agitator having a cylindrical rotor and shaft extending therefrom; inserting the agitator in a horizontally oriented cylindrical vessel and sealing the cylindrical vessel, the
5 cylindrical rotor being dimensioned to provide a gap of no greater than 3 mm between an outer surface of the rotor and an inner surface of the vessel; providing at least one port through the cylindrical vessel and maintaining the port at a highest point of the horizontally oriented cylindrical vessel; filling the cylindrical vessel with the dispersion until the dispersion drives out substantially all of the air in the
10 vessel; and rotating the agitator for a predetermined period.

The method further includes cooling the vessel by jacketing the vessel and flowing water between the jacket and the vessel. Another method comprises externally circulating the dispersion through a plurality of ports formed through the horizontally oriented vessel to thereby cool the dispersion or refresh the dispersion.
15

BRIEF DESCRIPTION OF THE DRAWINGS

These and other features, aspects, and advantages of the present invention will become more apparent from the following description, appended claims, and accompanying exemplary embodiments shown in the drawings.

20 Fig. 1 illustrates a small-scale or micro-media mill according to one embodiment of the present invention.

Fig. 1A illustrates an enlarged detailed view of the mill shown in Fig. 1.

Fig. 2 illustrates the media mill of Fig. 1, but with a different vessel.

Fig. 3 illustrates a small-scale or micro-media mill according to another
25 embodiment of the present invention.

Fig. 3A illustrates an enlarged detailed view of the mill shown in Fig. 3.

Fig. 3B illustrates an enlarged detailed view taken along area 3B of Fig. 3A.

Fig. 4 illustrates a side view of a small scale or micro media mill according to another embodiment of the present invention.

30 Fig. 5 illustrates another embodiment of an agitator and another embodiment

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of a vessel that can be used with the media mill of Figs. 1-4.

Fig. 6 illustrates the agitator of the type illustrated in the embodiments of Figs. 1-4.

Fig. 7-13D illustrate various agitator configurations that can be used with the media mill of Figs. 1-4.

DETAILED DESCRIPTION

Although references are made below to directions in describing the structure, they are made relative to the drawings (as normally viewed) for convenience. The directions, such as top, bottom, upper, lower, etc., are not intended to be taken literally or limit the present invention.

A small-scale mill 1, 1A, 2 (Figs. 1-4) according to the present invention is designed to mill relatively small amounts of dispersion to a size ranging from microns to nanometers in a relatively short time, i.e., a few hours or less, using attrition milling media, such as polymer type, e.g., cross linked polystyrene media, having nominal size no greater than about 500 microns (0.5 mm) to about 50 microns or mixtures of the sizes ranging between them. The performance of the present scale mill is designed to provide the results comparable to the DYNO-MILL and the NETZSCH ZETA mills. The mill 1, 1A, 2 according to the present invention can have a provision for cooling the dispersion, which allows increased agitator tip speed without overheating, to increase its efficiency and allow milling of heat sensitive pharmaceutical products.

A vertically oriented mills 1, 1A is exemplified in Figs. 1-3A. The mill 1, 1A generally comprises a container or vessel 10, 10A, 10B, 10C, an agitator or mixer 30, a coupling 50, and a rotatable journaled shaft 120, which can be that of a motor 100. The vessel 10, 10A, 10B, 10C has a substantially cylindrical milling chamber and can be single walled 10C, as shown in Figs. 5 and 6, or jacketed (double-walled) 10, 10A, 10B, as shown in Figs. 1-3A, to allow water cooling. The agitator 30, which comprises a rotor 32 and a shaft 40 extending from one end of the rotor 32, is preferably a single piece to ease cleaning, and is adapted to be connected to a

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conventional electric motor 100, which preferably is capable of rotating up to 6000 RPM. A conventional motor controller 101 (Figs. 1, 3, 4), such as SERVODYNE Mixer Controller available from Cole-Parmer Instrument Co. of Vernon Hills, Ill, can control the motor speed and duration. The coupling 50 is mounted to the motor
5 100 and is coupled to the vessel 10 using a sanitary fitting and a clamp C (shown in phantom in Fig. 3) to seal the vessel 10, 10A, 10B, 10C.

Referring to Fig. 1A, the vessel 10 in this embodiment is double walled or jacketed to circulate a coolant. Specifically, the vessel 10 comprises an inner cylindrical wall 12 and an outer cylindrical wall 14 spaced from and concentric with
10 the inner cylindrical wall 12. The outer wall 14, however, need not be cylindrical or concentric relative to the inner wall 12. It can have any configuration that allows water circulation to the inner cylindrical wall 12. An annular mounting flange 16 holds together top end of the inner and outer cylindrical walls 12, 14. The inner cylindrical wall 12 has a bottom wall 13 enclosing its bottom end to form an inner
15 vessel (12, 13). The outer cylindrical wall 14 also has a bottom wall 15 enclosing its bottom end and spaced from the bottom wall 13 to form an outer vessel (14, 15). The outer vessel (14, 15) is spaced from the inner vessel (12, 13) and forms a vessel shaped chamber 17 that can be filled with water and circulated to cool the dispersion during milling.

20 The outer cylindrical wall 14 has two openings 20, preferably positioned diametrically opposite to each other and a pair of coolant connectors 22 aligned with the openings 20. Either of these connectors 22 can serve as a coolant inlet or outlet. These connectors 22 can extend substantially radially outwardly. The free end of each connector can have a sanitary fitting, which includes an annular mounting
25 flange 24 and a complementary fitting (essentially mirror image thereof – not shown), adapted to be clamped with, for example, a TRI-CLAMP available from Tri-Clover Inc. of Kenosha, WI. These mounting flanges 24 are configured substantially similar to the mounting flanges 16, 52 connecting the vessel 10, 10A, 10B, 10C to the motor 100. All of these mounting flanges 16, 24, 52 can be adapted
30 for a TRI-CLAMP, as described below. Each of these flanges 16, 24, 52 has an

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annular groove G for seating an annular gasket 60 and a beveled or tapered surface B. The mounting flanges and the gasket 60, which is FDA approved, adapted for the TRI-CLAMP are also available from Tri-Clover Inc.

Fig. 2 shows another embodiment of the double walled vessel 10A, which is substantially similar to that shown in Figs. 1 and 1A. The difference is that the bottom wall 13 of the inner cylindrical wall 12 in Fig. 2 is exposed. In other words, the alternative vessel 10A of Fig. 2 has no outer bottom wall 15 of Fig. 1A. The alternative vessel 10A has its bottom wall 13 extending radially outwardly to the outer cylindrical wall 14. The chamber 17 is annular instead of being vessel shaped (Fig. 2). The bottom wall 13 can have a heat sink or a Peltier coolant (not shown) attached. The bottom wall 13 also can have an observation window or an opening 205, which can be sealed or can have a valve 210 that vents excess pressure build up and/or allows a sample withdrawal. This way, minute amounts of dispersion can be taken out and examined without having to take off the coupling 50. Alternatively, the opening can be sealed using a self-sealing resilient material that permits insertion of a syringe for withdrawing samples. The window 205 can have a small chamber extending outwardly from the bottom (not shown). This chamber can hold a small amount of dispersion so that it can be viewed through an observation device. This chamber can be configured so that the dispersion is constantly circulated, such as placing the window 205 in a location where the dispersion is constantly moving.

Figs. 3 and 3A show another embodiment of the double walled vessel 10B, which is substantially similar to that shown in Figs. 1 and 1A. The primary difference is that the outer bottom wall 15A can be threaded or screwed (or sealingly mounted) into the outer cylindrical wall 14. In this respect, the outer bottom wall 15A can have an annular groove (not numbered) that seats an O-ring 74 or the like to provide a better water seal. Another difference from the vessel of Figs. 1 and 1A, is that a quick couple fitting 22A, 24A, 24B is used. The connectors 22A are threadingly mounted to the openings 20 formed in the outer cylindrical wall 14. The connectors 22A can use a commercially available quick connector or couple 24A, such as 1/8" PARKER series 60 Quick Couple. The quick couple 24A can be

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connected to a flexible hose barb 24A, such as a commercially available stainless steel 1/8" NPT x 1/4" hose barb. The double-walled vessels 10 and 10A can also use the quick couple fitting 22A, 24A, 24B instead of the sanitary fitting type described above and illustrated in Figs. 1-2.

- 5 Alternative to the double walled vessel is a single walled vessel 10C shown in Figs. 5 and 6. The single walled vessel 10C can be used when the product to be milled is not heat sensitive or for milling a short period. The single walled vessel is constructed similar to the inner vessel (12, 13) of the double walled vessel 10. A heat sink (not shown) can be attached to its cylindrical wall 12 and bottom wall 13.
- 10 The heat sink also can be fan cooled. Another alternative cooling system can be a Peltier cooler, which operates on the Peltier effect theory (cooling by flowing an electric current through a Peltier module made of two different types of conductive or semiconductive materials attached together). A Peltier module with a heat sink (Peltier coolant) can be detachably attached to the vessel.
- 15 In the embodiments of Figs. 1-3, 5, and 6, the mounting flange 52 of the coupling 50 is configured substantially the same as or complementary to the annular mounting flange 16. The mounting flanges 16 and 52 are coupled facing each other with the gasket 60, such as a Tri-Clamp EPDM black, FDA approved gasket, sandwiched therebetween, as shown in Figs. 1A, 2, and 3A. The gasket 60 has
- 20 annular lower 62 and upper 64 protrusions that engage the respective grooves G formed in the mounting flanges 16, 52, and align the flanges 16 and 52. A TRI-CLAMP C (see Fig. 3) can engage the periphery P and the beveled surfaces B of the mounting flanges 16, 52. When these flanges are aligned, they form a trapezoidal profile. Tightly wrapping the TRI-CLAMP around the periphery and the beveled
- 25 surfaces B squeezes the flanges 16, 52 together to provide a sealed connection.

The mounting flanges 24 of the connectors 22 (Figs. 1, 1A, 2) can be connected to their respective water source and drain pipes (not shown) in the same way as the vessel 10, 10A, 10B, 10C is connected to the coupling 50, as just described, using a gasket 60 and a TRI-CLAMP C.

- 30 Referring to the embodiments of Figs. 1-3A, the coupling 50 also has a

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cylindrical portion 54 extending from its mounting flange 52. The flange 52 has a central opening 56 and a stepped recess 58 concentric with the opening 56. The recess 58 seats a seal, which can be a lip or mechanical seal ring 70 having a complementary configuration. Specifically, the seal ring 70 can be made from PTFE with a Wolastonite filler and can have an L-shaped (cross-sectional) profile as shown in detail in Fig. 3B. The seal ring 70 also can include a concentric O-ring 71 or the like, as shown in Fig. 3B. The opening 56 is dimensioned only slightly larger than the agitator's shaft 40. The seal ring 70 is adapted to engage the shaft 40 and seal the same while permitting the agitator 30 to rotate.

Referring to Figs. 1A, 2, 3A, the cylindrical portion 54 is threaded on its inner side so that it can be attached to the motor 100. Specifically, the coupling 50 is attached to a shaft mount 110, which comprises an annular flange 112 and a downwardly extending cylindrical member 114. The cylindrical member 114 has an outer threading for threadingly mating with the threaded cylindrical portion 54 of the coupling 50. The flange 112 is mounted to the motor using bolts 200 or the like. The motor 100 can be mounted to a stand or fixture 150 via the flange 112, using bolts 200. The stand 150 allows the motor 100 and the vessel 10, 10A, 10B, 10C to be oriented vertically, as shown in Figs. 1, 1A, 2, and 3.

The shaft mount 110 has a central through hole 115 dimensioned larger than the shaft 40. The distal (lower) end of the cylindrical member 114 has an annular projection 116 that bears against the seal ring 70 (see Fig. 3B) and holds the seal ring 70 in place. The coupling 50 has an annular end face 55 that abuts against a complementary face or shoulder 117 formed on the distal (lower) end of the cylindrical member 114, adjacent to the annular projection 116. The end face 55 provides a positive stop and maintains proper seal compression when the coupling 50 is mounted to the shaft mount 110. In this respect, referring to Fig. 3A, the mounting flange 52 can also include an O-ring 72 positioned in an annular groove 59 formed on the upper end face 55 to provide additional seal. As the temperature of the dispersion increases during milling, expanding air under pressure is designed to escape through the seal ring 70, while maintaining liquid seal. In this respect, the

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cylindrical member 114 has a vent opening 118 to vent any air seeping through the seal ring 70.

The rotor shaft 40 comprises a larger diameter portion 42 and a smaller diameter portion 44 having a threaded free end 45. A tapered section 46 extends
5 between these portions 42, 44. The rotor 30 is attached to the motor 100 by inserting the smaller diameter portion 44 into a hollow motor shaft 120 and threading a nut 49 or a manual knob 49A (Fig. 3) onto the threaded end 45, which tightly pulls the tapered section 46 against the lower end or mouth of the hollow shaft 120, compressively attaching the agitator shaft 40 to the hollow motor shaft 120. The nut
10 49 or the knob 49A can be covered with a safety cap 47 (Fig. 3), which can be mounted to the top end of the motor 100 using a base 48. The cap 47 can be threadedly mounted to the base 48. The tapered section 46 also eases the insertion of the shaft 40 through the seal ring 70 and prevents tear or damage to the seal ring 70. At least around a section CP of the large diametered shaft portion 42 contacting
15 the seal 70 is preferably coated with a wear resistant coating, such as a hard chrome coating to prevent wear.

Although the above-described mill 1 (Figs. 1-3B) has been described and shown in a vertical configuration, the present invention also contemplates a horizontally oriented mill 2, as shown in Fig. 4. The horizontally oriented mill 2 is
20 substantially similar to the vertically oriented mill 1 shown in Figs. 1-3, except for the vessel and coupling configuration. In the horizontally oriented mill, a mounting bracket 160 is attached to the motor 100 via the shaft mount 110 so that the mill 2 is stably supported in the horizontal position, as shown in Fig. 4. In the horizontally oriented mill 2, its vessel 10D can be attached to the motor via a threaded coupling
25 16', and the shaft 40 can be sealed via a single or double mechanical seal, or a lip seal 70' (shown in phantom).

Referring to Fig. 4, the vessel 10D for the horizontally oriented mill 2 is substantially similar to the singled walled vessel 10C (Fig. 5 and 6), except that the flange 16 (Figs. 5 and 6) has a threaded coupling 16', substantially similar to the
30 threaded coupling 50 shown in Figs. 1-3A. The vessel 10D has an open cylindrical

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wall 12, with one closed by an end wall 13. The threaded coupling 16' is integrally or monolithically formed at the opposite open end. The vessel 10D, however, can be configured like the singled walled vessel 10C for use with the afore-described sanitary fitting.

5 The vessel 10D is illustrated with four fill/drain/cooling ports P1-P4 for illustrative purposes only. Only one port is needed in the horizontally oriented mill 2. The ports P2-P4 are radially extending through the cylindrical wall 12 of the vessel 10B, whereas the port P1 is axially extending from the end wall 13 of the vessel 10B. In one embodiment, the vessel 10D can have a single top fill port P2 or
10 P3. In such an embodiment, it is especially desirable for the top port P2 or P3 to be located at or along the highest point of the milling chamber, i.e., at 12 O'clock position for a cylindrical vessel 10D, as this allows the chamber to be filled so that all of the air is displaced from the chamber. The absence of air in the milling chamber during operation prevents the formation of foam and enhances milling
15 performance.

 Alternatively, the horizontally oriented vessel 10D can contain two or more ports, such as two top radial ports P2 and P3, a single axial port P1 and a single top radial port P3, or a single top radial port P3 and a single bottom radial port P4. In such embodiments, the dispersion can be externally circulated through the vessel
20 10D, where one port acts as an outlet and the other an inlet. The dispersion can be cooled or replenished during the circulating process. Using two ports, one can recirculate (or add) the process fluid and/or attrition media via an external vessel and pump (not shown). If the attrition media has to remain in the vessel, the outlet port can be fitted with a suitable screen or filter to retain the media during operation.

25 Referring to Figs. 5-13D, the rotor 32, 32A-32J (collectively "32") for both the vertically and horizontally oriented mills 1, 1A, 2 can have different geometric configurations. The agitator 30 is preferably made of stainless steel or teflon or stainless steel with a teflon coating. In this respect, the TRI-CLAMP can be made of 304 stainless steel. The components that are exposed to the dispersion also can be
30 made of 316 stainless steel. In fact, all of the metal components, except the clamp

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and the motor can be made of 316 stainless steel. Alternatively, all metal components that become exposed to the dispersion can be made of any material that is resistant to crevice corrosion, pitting, and stress corrosion, such as an AL-6XN stainless steel alloy. An AL-6XN alloy meets ASME and ASTM specifications, and
5 is approved by the USDA for use as a food contact surface.

The rotor 32 also can comprise a variety of geometries, surface textures, and surface modifications, such as channels or protrusions to alter the fluid flow patterns. For example, the rotor 32 can be cylindrical (straight), as shown in Fig. 5, or cylindrical (tapered ends T1, T2) as shown in Figs. 1-4 and 6. In other illustrated
10 embodiments, the rotor 32 can be hexagonal (Fig. 7), ribbed (Fig. 8), square (Fig. 9), cylindrical with channels (Figs. 10 and 11), cylindrical with passageways (Fig. 12), and cylindrical with a cavity and slots (Figs. 13-13D). All of these embodiments can have tapered end surfaces T1, T2.

Specifically, the hexagonal rotor 32A (Fig. 7) has six planar sides 202. The
15 ribbed rotor 32B (Fig. 8) has hexagonal sides 202 as shown in Fig. 7, but with six ribs 204 extending respectively from the middle of each of the six sides 202. The square rotor 32C (Fig. 9) has four planar sides 206. The cylindrical rotor 32D (Fig. 10) has four channels 208 that are perpendicular to each adjacent channels 208. The cylindrical rotor 32E (Fig. 11) is substantially identical to the cylindrical rotor 32D
20 of Fig. 10, but has six channels 208 instead of four, symmetrically angled and spaced apart. The cylindrical rotor 32F (Fig. 12) has four angled passageways 210, extending from the tapered or conical end surfaces T1, T2. These angled passageways have four openings at the first tapered end surface T1 and four openings at the second tapered end surface T2. An imaginary circle intercepting the
25 four openings at the first tapered end surface T1 has a greater diameter than an imaginary circle intercepting the four openings at the second tapered end surface T2.

The cylindrical rotors 32G, 32H, 32I, 32J (Figs. 13-13D) each have a concentric cylindrical cavity 212 opening to the second tapered surface T2. Depending on the material and the media mill size, these rotors can have at least
30 three (not shown) equally spaced apart axially extending flow modifying channels

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214. The rotors 32G-23J are respectively shown with four, six, eight, and nine channels 214. These slots 214 can also be angled as shown, or spiraled or helically configured (not shown) relative to the rotational axis. In the embodiment of Fig. 13A, four channels 214 can be angled 90° relative to the adjacent channels. In the
5 embodiment of Fig. 13B, the six channels 214 can be angled 60°. In the embodiment of Fig. 13C, the eight channels 214 can be angled 45°. In the embodiment of Fig. 13D, the nine channels 214 can be angled 40° relative to the vertical. In alternative embodiments (not shown), the channels 214 can radially extend from the axis of the rotor 41.
- 10 The rotors 32G-32J of Figs. 13A-13D can act as a pump. That is, these rotors can withdraw fluid into the cavity 212 and eject fluid outwardly through the channels 214, or conversely withdraw fluid into the cavity through the channels 214 and eject fluid outwardly through the cavity 212, depending on the direction of the rotation, to modify the dispersion flow pattern.
- 15 In other embodiments (not shown), rotors also can contain pegs, agitator discs, or a combination thereof.
- Referring to the cylindrical rotor 32 shown in Figs. 1-6, its outer peripheral cylindrical surface 36 and the inner cylindrical surface 12" of the inner cylindrical wall 12 of the vessel 10, 10A, 10B, 10C, 10D are dimensioned to provide a small
20 gap X. The gap X is preferably no greater than 3 mm and no smaller than 0.3 mm. In general, this gap X should be approximately 6 times the diameter of the milling media, which is preferably made of cross linked polystyrene or other polymer as described in U.S. Patent No. 5,718,388 issued to Czekai, *et al.* The largest attrition milling media preferably is nominally sized no greater than 500 microns (0.5 mm).
- 25 Presently, the smallest attrition milling media contemplated is about 50 microns. Nonetheless, it is envisioned that a smaller attrition milling media can be suitable for milling certain non-soluble products, such as pharmaceutical products, which means that the gap X can be made smaller accordingly.
- The vessel size can vary for milling small amounts of dispersion. Although
30 the present invention is not limited to particular sizes, in the preferred embodiment,

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the inner diameter of the vessel is between 5/8 inch to 4 inches. By way of examples only, milling chamber of the vessel 10, 10A, 10B, 10C, and 10D and the cylindrical rotor 32 can have the dimensions specified in Tables 1 and 2.

| TABLE 1 (STRAIGHT ROTORS) | | | |
|---|-----------|-----------|-----------|
| CYLINDRICAL VESSEL Size | #1 | #2 | #3 |
| TRI-CLAMP Size VESSEL/COUPLING | 2" TC | 2.5" TC | 3" TC |
| R-vessel (inch) (1/2 DC) | 0.685 | 0.935 | 1.185 |
| H-vessel (inch) (HC) | 1.125 | 1.125 | 1.125 |
| R-rotor (inch) (1/2 DR) | 0.567 | 0.817 | 1.063 |
| H-rotor (inch) (HR) | 0.890 | 0.890 | 0.890 |
| R-shaft (inch) (1/2 DS) | 0.313 | 0.313 | 0.313 |
| H-shaft (inch) (HS) | 0.118 | 0.118 | 0.118 |
| Volume Vessel (in ³) | 1.658 | 3.090 | 4.963 |
| Volume Rotor (in ³) | 0.899 | 1.866 | 3.156 |
| Volume Shaft (in ³) | 0.036 | 0.036 | 0.036 |
| Working Volume (in ³) | 0.723 | 1.187 | 1.770 |
| | 11.855 ml | 19.458 ml | 29.012 ml |
| Typical Dispersion Volume @ 50% media charge | 8.299 ml | 13.621 ml | 20.309 ml |
| Typical Dispersion Volume @ 90% media charge | 5.453 ml | 8.951 ml | 13.346 ml |

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| TABLE 2 (TAPERED ROTORS) | | | |
|-----------------------------------|-------|---------|-------|
| VESSEL Size | #1 | #2 | #3 |
| TRI-CLAMP Size VESSEL/COUPLING | 2" TC | 2.5" TC | 3" TC |
| R-vessel (inch) (1/2 DC) | 0.685 | 0.935 | 1.185 |
| H-vessel (inch) (HC) | 1.190 | 1.190 | 1.190 |
| R-rotor (inch) (1/2 DR) | 0.567 | 0.817 | 1.063 |
| H-rotor (inch) (HR) | 1.018 | 1.018 | 1.018 |
| H-top taper (inch) (HTT) | 0.064 | 0.120 | 0.120 |
| H-bottom taper (inch) (HBT) | 0.064 | 0.075 | 0.075 |
| R-shaft (inch) (1/2 DS) | 0.313 | 0.313 | 0.313 |
| H-shaft (inch) (HS) | 0.086 | 0.086 | 0.086 |

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| TABLE 2 (TAPERED ROTORS) | | | |
|---|-----------|-----------|-----------|
| Volume Vessel (in ³) | 1.754 | 3.268 | 5.250 |
| Volume Rotor Body (in ³) | 0.899 | 1.726 | 2.919 |
| Volume Upper Cone (in ³) | 0.040 | 0.128 | 0.196 |
| Volume Lower Cone (in ³) | 0.040 | 0.080 | 0.122 |
| Volume Shaft (in ³) | 0.026 | 0.026 | 0.026 |
| Volume Complete Rotor (in ³) | 0.979 | 1.934 | 3.237 |
| Working Volume (in ³) | 0.749 | 1.308 | 1.986 |
| | 12.274 ml | 21.429 ml | 32.548 ml |
| Typical Dispersion Volume @ 50% media charge | 8.592 ml | 15.001 ml | 22.784 ml |
| Typical Dispersion Volume @ 90% media charge | 5.646 ml | 9.858 ml | 14.972 ml |

It was mentioned that the gap X between the rotor 32 and the inner surface 12" of the cylindrical wall 12 should be approximately 6 times the diameter of the attrition milling media. Nonetheless, the vessel and rotor combination can be used with 50, 200, 500 and mixtures of 50/200, 50/500, or 50/200/500 micron media. These milling media also can be used with a gap X of 1 mm. The rotor speed is correlated to the rotor diameter to produce different tip speeds, which are related to the milling action. A too high tip speed can generate much heat and can evaporate the dispersion. A too low tip speed causes inefficient milling.

Tapering the ends of the rotor 32, as illustrated in Figs. 1-4 and 6-13D can provide more uniform shear throughout the milling chamber. Although the shear rate between two concentric cylinders is relatively constant if the gap is narrow, a flat end (bottom or top) surface cylinder will produce less uniform shear stress. Referring to Fig. 6, by equating the shear rate for concentric cylinders and a cone shape surface T2 revolving about a flat bottomed vessel surface 13", one can calculate a tip angle $\beta = \arctan(1 - DR/DC)$, where DR represents an outer cylindrical surface 36 of the rotor 32 and DC represents an inner cylindrical surface 12" of the vessel 10, 10A, 10B, 10C, 10D. Ideally, the cone should "touch" the

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bottom (or the top or the ends) to maintain a constant shear. This, however, is not practical. Instead, a cone is truncated, forming a gap d between the truncated bottom surface T2 and the opposing bottom vessel surface 13". The gap d is preferably defined by $DT/2 \times \tan\beta$, where $DT/2$ is the distance between the center of rotation and the truncation edge. If $DT/2$ is sufficiently small in comparison with $DR/2$, a substantially uniform shear can be maintained. A uniform shear rate would allow the user to better estimate shearing effect in the milling of colloidal dispersions, although constant shear in the mill is not necessary to produce a colloidal dispersion. Another benefit to having a tapered bottom surface T2 is that it prevents the accumulation of suspended particles on the bottom near the center of rotation where the speed is at its minimal.

U.S. Patent Nos. 5,414,786 issued to Liversidge, *et al.*, 5,518,187 issued to Bruno, *et al.*, and 5,718,388 and 5,862,999 issued to Czekai, *et al.* disclose milling pharmaceutical products using polymeric milling media. These patents further disclose dispersion formulations for a wet media milling. The disclosures of these patents are incorporated herein by reference.

In operation of the vertically oriented mill 1, 1A, an appropriate dispersion formulation containing the milling media and the product to be milled is prepared, which can be prepared according to the aforementioned patents. The dispersion is poured into the vessel 10, 10A, 10B, 10C to a level that would cause the dispersion to fill to the brim or the top face 61 (see Figs. 5 and 6) of the gasket 60 (or even overflow) when the rotor 30 fully inserted to the vessel 10 to minimize trapping of air within the vessel. After filling appropriate amount of the dispersion into the vessel 10, 10A, 10C, the vessel is aligned with the coupling 50, which is premounted to the shaft mount 110, and raised until the vessel and coupling flanges 16, 52 line up. The aligned coupling flanges 16, 52 are held together using, for instance, a TRI-CLAMP C or the like, which couples the vessel 10, 10A, 10B, 10C to the coupling 50 and seals the dispersion. Similarly, the connectors 22, 22A are connected to a coolant inlet and outlet respectively using two TRI-CLAMPs or quick coupling 24A, one for each connector 22, 22A. Coolant, such as water, is circulated to cool the

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vessel 10, 10A, 10B, 10C. The motor controller 101 can be set to rotate the rotor for a predetermined period, depending on the dispersion formulation.

Because the coupling 50 seals the vessel 10, 10A, 10B, 10C, and because only a very small amount of air is trapped in the vessel, vortexing and contamination problems are minimized or avoided. Thus, the mill according to the present invention can prevent the dispersion formulation from foaming. Further, because the vessel is cooled, either by the cooling jacket or by circulating the dispersion, the rotor 32 can be spun faster. Thus, a higher energy can be transferred to the dispersion.

10 In the operation of the horizontally oriented mill 2, the vessel 10D is first mounted to the shaft mount 110 with either a threaded coupling 16' (as shown in Fig. 4) or a sanitary fitting (as shown in Figs. 1-3) and with the rotor 32 positioned inside the vessel 10D as shown in Fig. 4. The dispersion formulation containing the milling media and the product to be milled is poured or injected through the top port P2 or P3 (only one being required) until all or substantially all of the air is displaced with the dispersion. The motor controller 101 then can be set to rotate the rotor 32 for a predetermined period, depending on the dispersion formulation. If the vessel 10D has multiple ports, such as P1, P3 or P2, P3, or P3, P4, the dispersion can be circulated via an external vessel and pump (not shown) during milling.

20 Because virtually all or substantially all of the air can be displaced in the horizontally oriented mill 2, vortexing and contamination problems are minimized or avoided. Thus, the mill according to the present invention can prevent the dispersion formulation from foaming. Further, because the dispersion can be circulated, where it can be cooled with external cooling system, the rotor can be spun faster and high energy can be transferred to the dispersion. Moreover, the dispersion can be refreshed or made in batches or inspected without having to disassemble the vessel 10D from the shaft mount 110.

The pharmaceutical products herein include those products described in the aforementioned patents incorporated herein by reference and any human or animal ingestable products and cosmetic products.

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Given the disclosure of the present invention, one versed in the art would appreciate that there may be other embodiments and modifications within the scope and spirit of the present invention. Accordingly, all modifications attainable by one versed in the art from the present disclosure within the scope and spirit of the present
5 invention are to be included as further embodiments of the present invention. The scope of the present invention accordingly is to be defined as set forth in the appended claims.

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WHAT IS CLAIMED IS:

1. A small-scale mill for milling a non-soluble product contained in a dispersion containing attrition milling media, comprising:
 - a shaft mount;
 - a rotatable shaft mounted for rotation about the shaft mount;
 - a relatively small vessel having an opening;
 - an agitator having a rotor and a rotor shaft extending from the rotor, the shaft being connected to the rotatable shaft and the rotor being dimensioned to be inserted in the vessel with a small gap formed between an outer rotating surface of the rotor and an internal surface of the vessel;
 - a coupling detachably connecting the vessel to the shaft mount, the coupling having an opening through which the rotor shaft extends, wherein the shaft mount sealing the vessel opening to seal the dispersion in the vessel.
2. A small-scale mill according to claim 1, further including a cooling system connected to the vessel.
3. A small scale mill according to claim 2, wherein the vessel comprises a cylindrical inner vessel and an outer vessel spaced from and surrounding the inner vessel and forming a chamber therebetween, and a flange connecting the ends thereof, the outer vessel having at least first and second passages that communicate with the chamber, the cooling system comprising the outer vessel with the first and second passages, which is adapted to circulate cooling fluid.
4. A small-scale mill according to claim 2, wherein the cooling system comprises a plurality of ports on the vessel for circulating the dispersion.
5. A small-scale mill according to claim 1, wherein the vessel is vertically oriented.

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6. A small-scale mill according to claim 1, wherein the vessel is horizontally oriented.
7. A small-scale mill according to claim 1, wherein the coupling has a threaded portion for detachably mounting to the shaft mount and a flange portion for detachably coupling to the vessel.
8. A small-scale mill according to claim 7, wherein the coupling is integrally formed with the vessel and has a threaded portion for detachably mounting to the shaft mount.
9. A small-scale mill according to claim 6, wherein the vessel includes at least one port through which the dispersion is filled.
10. A small-scale mill according to claim 6, wherein the vessel includes at least two ports through which the dispersion is circulated.
11. A small-scale mill according to claim 1, wherein the shaft is a motor shaft of a motor, wherein the motor is a variable speed motor and has a top speed of 6000 RPM.
12. A small-scale mill according to claim 1, wherein the rotor is cylindrical and the vessel is cylindrical, the small gap being no larger than 3 mm.
13. A small-scale mill according to claim 12, wherein the rotor is cylindrical and the vessel is cylindrical, the small gap being no larger than 1 mm.
14. A small-scale mill according to claim 12, wherein the cylindrical rotor has tapered end surfaces.

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15. A small-scale mill according to claim 14, wherein the cylindrical rotor has a cavity and a plurality of slots that extend between an inner surface of the cavity and an outer surface of the cylindrical rotor.
16. A small-scale mill according to claim 14, wherein the cylindrical rotor has a plurality of channels extending to an outer surface of the cylindrical rotor.
17. A small-scale mill according to claim 14, wherein the cylindrical rotor has a plurality of passageways extending between the tapered end surfaces of the cylindrical rotor.
18. A small-scale mill according to claim 1, wherein the attrition media comprises polystyrene having a nominal size of no larger than 500 microns.
19. A small-scale mill according to claim 1, wherein the attrition media comprises polystyrene having a nominal size no larger than 200 microns.
20. A small-scale mill according to claim 1, wherein the attrition media comprises polystyrene having a nominal size of about 50 microns.
21. A small-scale mill according to claim 1, wherein the attrition media comprises polystyrene having a mixture of nominal sizes of about 50 and 200 microns.
22. A small-scale mill according to claim 1, wherein the attrition media is a mixture having nominal sizes of about 50 and 500 microns.
23. A small-scale mill for milling a non-soluble product contained in a dispersion containing attrition milling media, comprising:
 - an inner cylindrical wall having a bottom and an open top;

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an outer cylindrical wall spaced from and surrounding the inner cylindrical wall, the inner and outer cylindrical walls being connected together so that a chamber is formed therebetween;

at least first and second passages that communicate with the chamber and adapted to pass coolant;

an agitator dimensioned to be inserted in the vessel through the open top;

a coupling that closes the open top, the coupling having an opening through which a portion of the agitator extends upwardly;

a seal that seals the portion of the agitator while permitting the agitator to rotate; and

a motor connected to the portion of the agitator extending through the coupling.

24. A small-scale mill according to claim 23, wherein the bottom extends radially and covers the bottom end of the outer cylindrical wall, the chamber being annular.

25. A small-scale mill according to claim 24, wherein the bottom has an aperture that allows samples of the dispersion to be withdrawn.

26. A small scale mill according to claim 25, further including a valve closing the aperture.

27. A small-scale mill according to claim 24, wherein the bottom has an observation window for observing the dispersion.

28. A small-scale mill for milling a non-soluble product contained in a dispersion containing 500 micron attrition milling media, comprising:

a shaft mount;

a rotatable shaft mounted for rotation about the shaft mount;

a relatively small vessel having an opening;

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an agitator having a rotor and a rotor shaft extending from the rotor, the shaft being connected to the rotatable shaft and the rotor being dimensioned to be inserted in the vessel with a small gap no greater than 3 mm formed between an outer rotating surface of the rotor and an internal surface of the vessel;

a coupling detachably connecting the vessel to the shaft mount, the coupling having an opening through which the rotor shaft extends, wherein the shaft mount sealing the vessel opening to seal the dispersion in the vessel.

29. A small scale mill according to claim 28, further including a cooling system that cools the vessel.

30. A small-scale mill according to claim 28, wherein the rotor is cylindrical and has tapered end surfaces.

31. A method of milling a non-soluble product, comprising:

providing a dispersion containing a non-soluble product to be milled and attrition milling media having a nominal size of no greater than 500 microns;

inserting the dispersion into a cylindrical vessel;

providing an agitator and a coupling that closes the vessel, the coupling having an opening through which a portion of the agitator extends, the agitator comprising a cylindrical rotor and a shaft extending therefrom, wherein the cylindrical rotor is dimensioned so that an outer periphery is no greater than 3 mm away from an inner surface of the cylindrical wall;

inserting an agitator into cylindrical vessel and sealingly closing the coupling, wherein the vessel is filled so that the dispersion eliminates substantially all of the air in the vessel when the agitator is fully inserted into the vessel; and

rotating the agitator for a predetermined period.

32. A method according to claim 31, further including cooling the vessel.

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33. A method according to claim 32, wherein the vessel is cooled by jacketing the vessel and flowing water between the jacket and the vessel.
34. A method of milling a non-soluble product, comprising:
providing a dispersion containing a non-soluble product to be milled and attrition milling media having a nominal size of no greater than 500 microns;
providing an agitator having a cylindrical rotor and shaft extending therefrom;
inserting the agitator in a horizontally oriented cylindrical vessel and sealing the cylindrical vessel, the cylindrical rotor being dimensioned to provide a gap of no greater than 3 mm between an outer surface of the rotor and an inner surface of the vessel;
providing at least one port through the cylindrical vessel and maintaining the port at a highest point of the horizontally oriented cylindrical vessel;
filling the cylindrical vessel with the dispersion until the dispersion drives out substantially all of the air in the vessel; and
rotating the agitator for a predetermined period.
35. A method according to claim 34, further including cooling the vessel.
36. A method according to claim 34, further including externally circulating the dispersion.
37. A small-scale mill according to claim 1, wherein the non-soluble product is a pharmaceutical product.
38. A small-scale mill according to claim 23, wherein the non-soluble product is a pharmaceutical product.
39. A small-scale mill according to claim 28, wherein the non-soluble product is

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a pharmaceutical product.

40. A method according to claim 31, wherein the non-soluble product is a pharmaceutical product.

41. A method according to claim 34, wherein the non-soluble product is a pharmaceutical product.

42. A small-scale mill of claim 1, wherein the attrition media is polymeric.

43. A small-scale mill of claim 23, wherein the attrition media is polymeric.

44. A small-scale mill of claim 28, wherein the attrition media is polymeric.

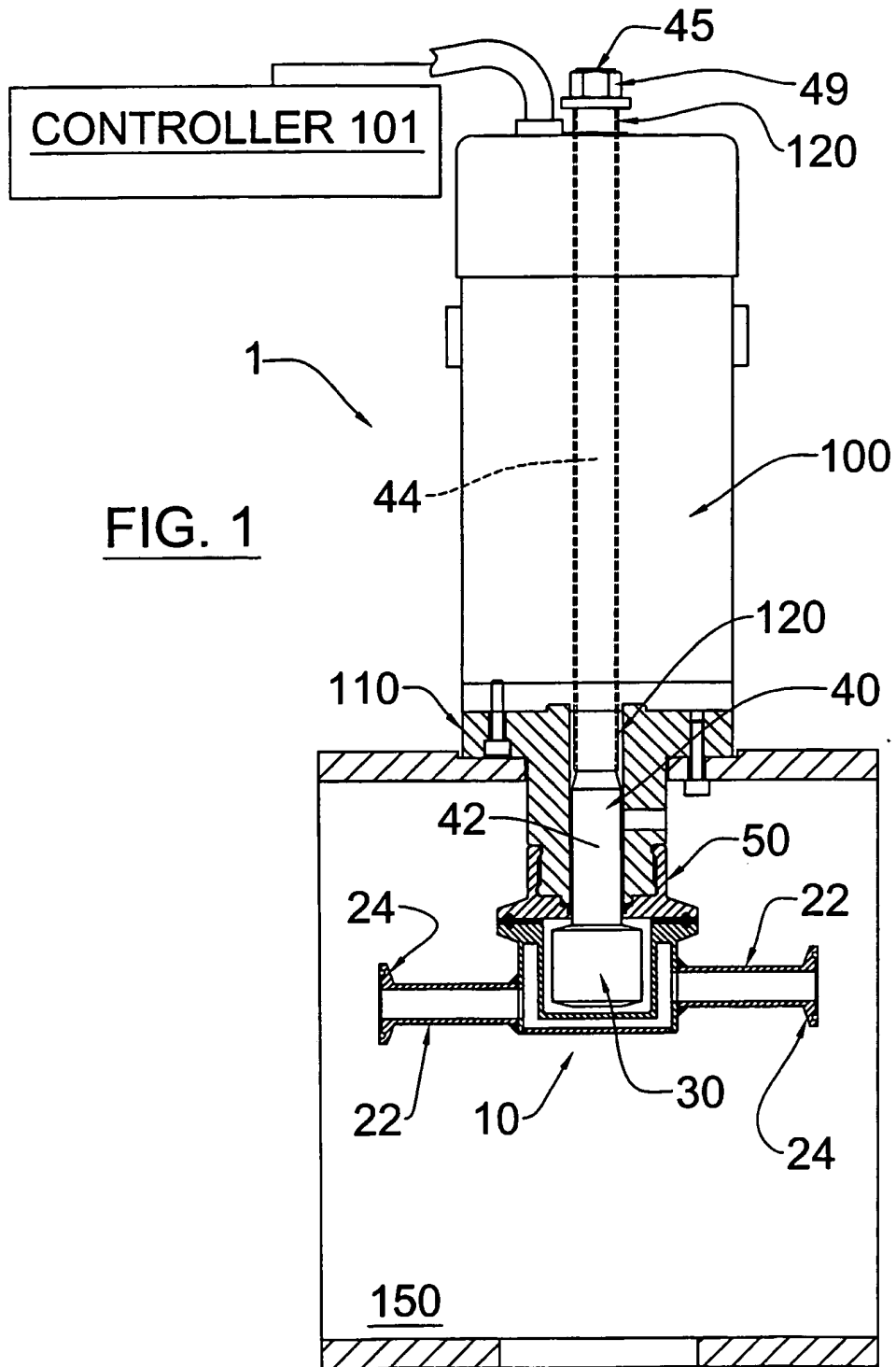
45. A method of claim 31, wherein the attrition media is polymeric.

46. A method of claim 34, wherein the attrition media is polymeric.

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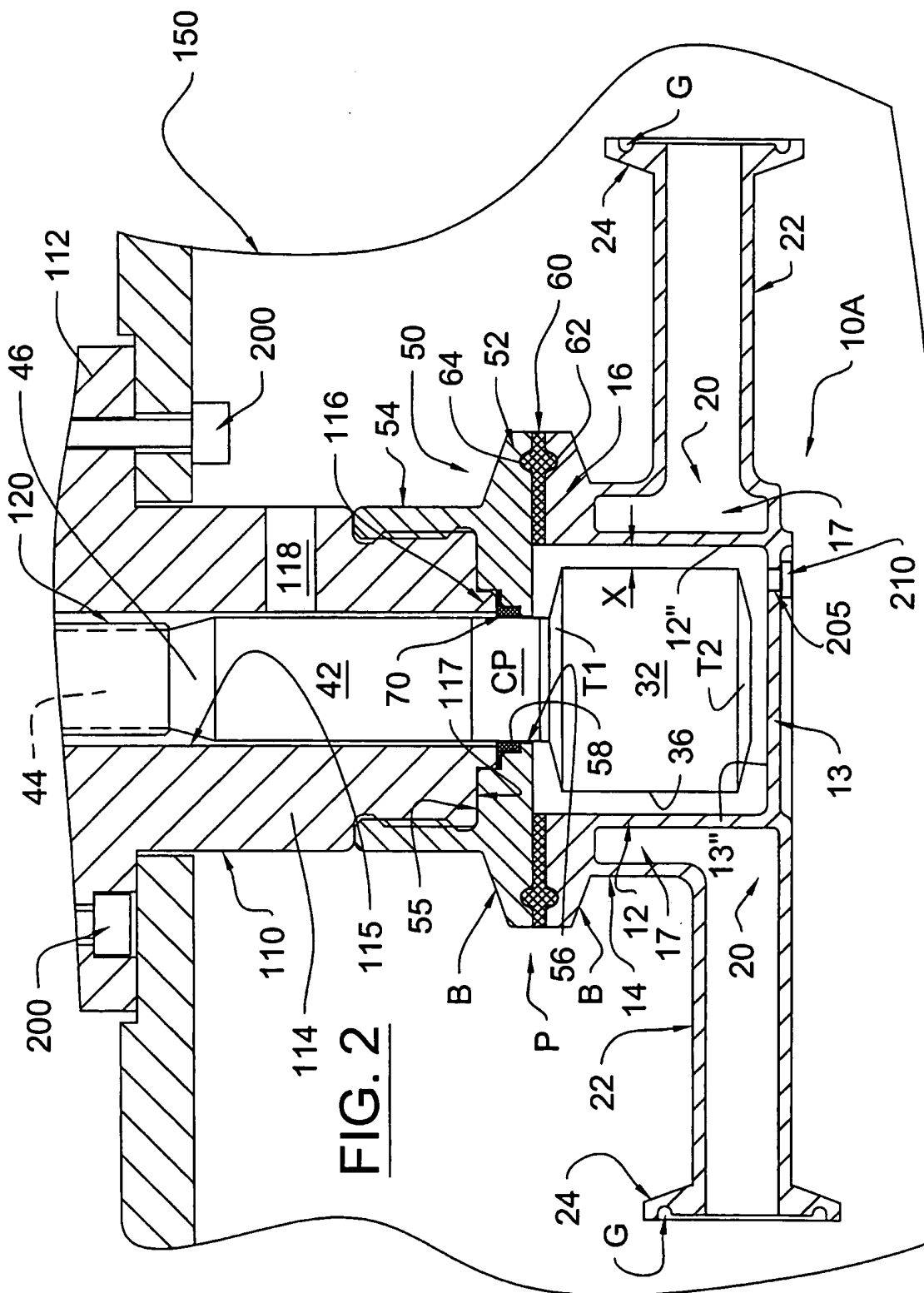


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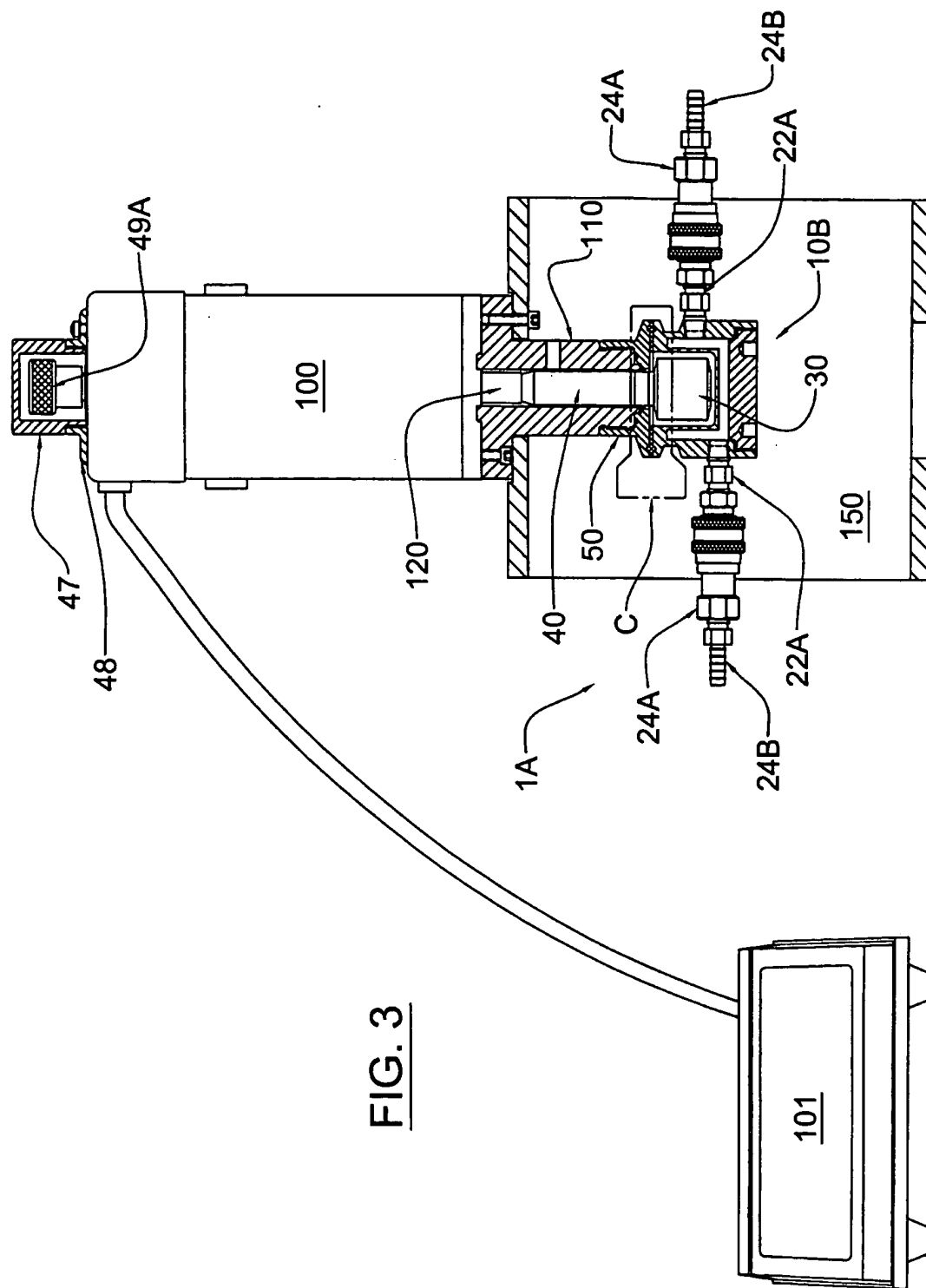
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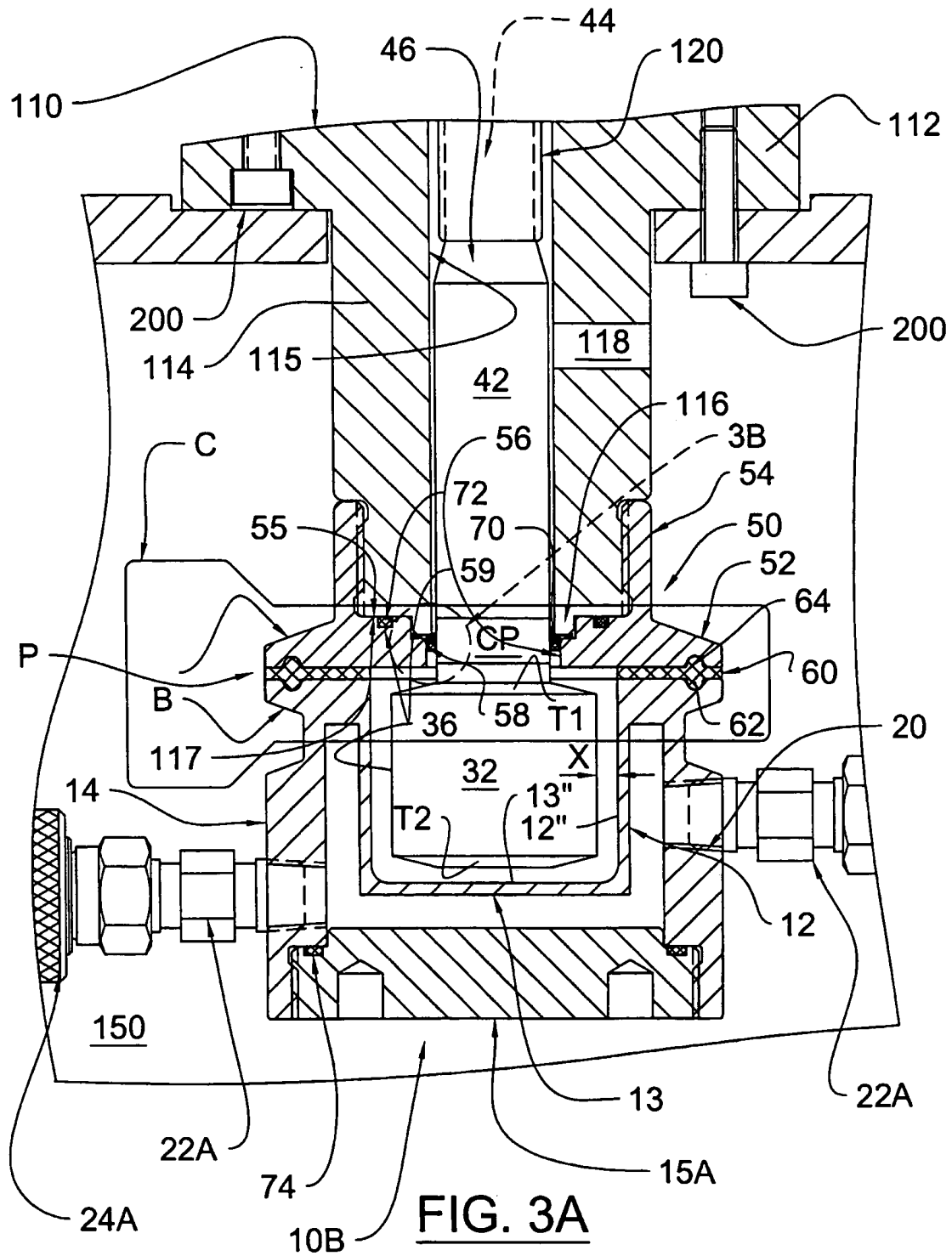
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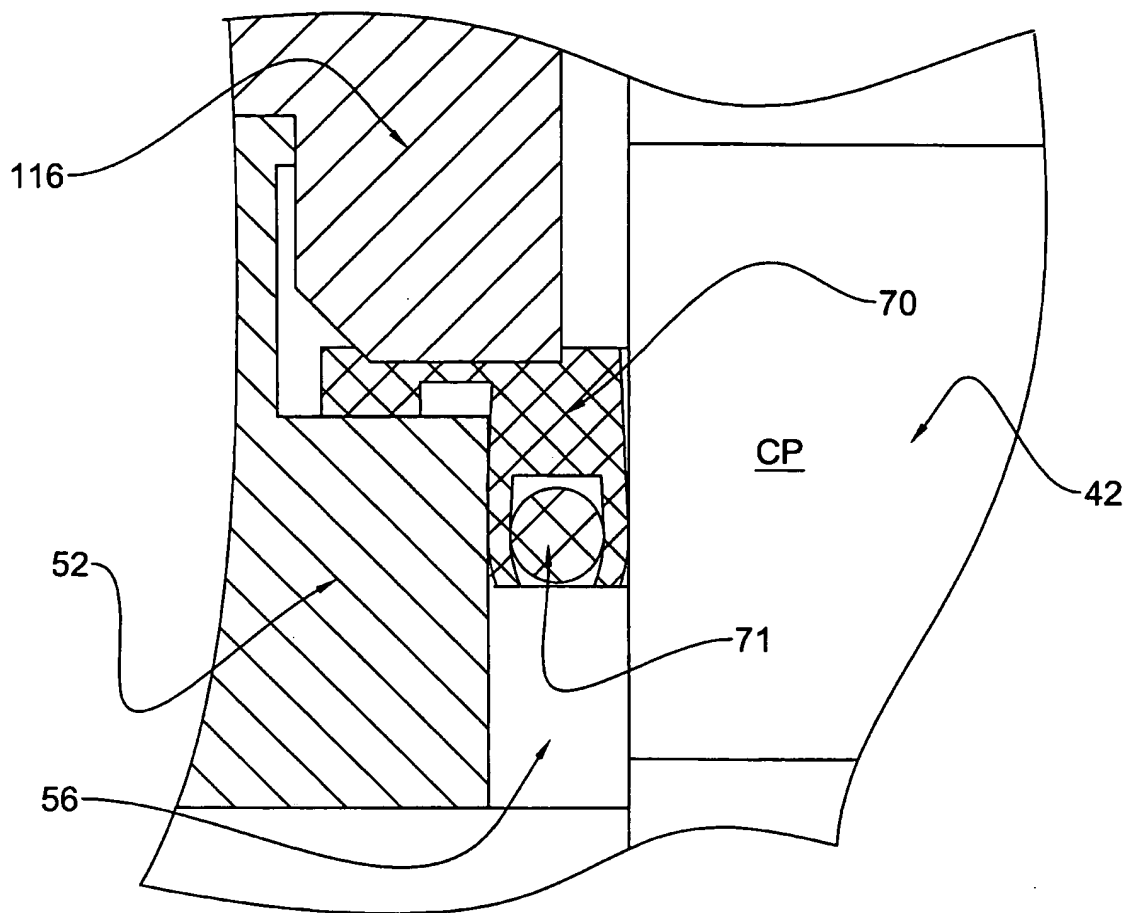
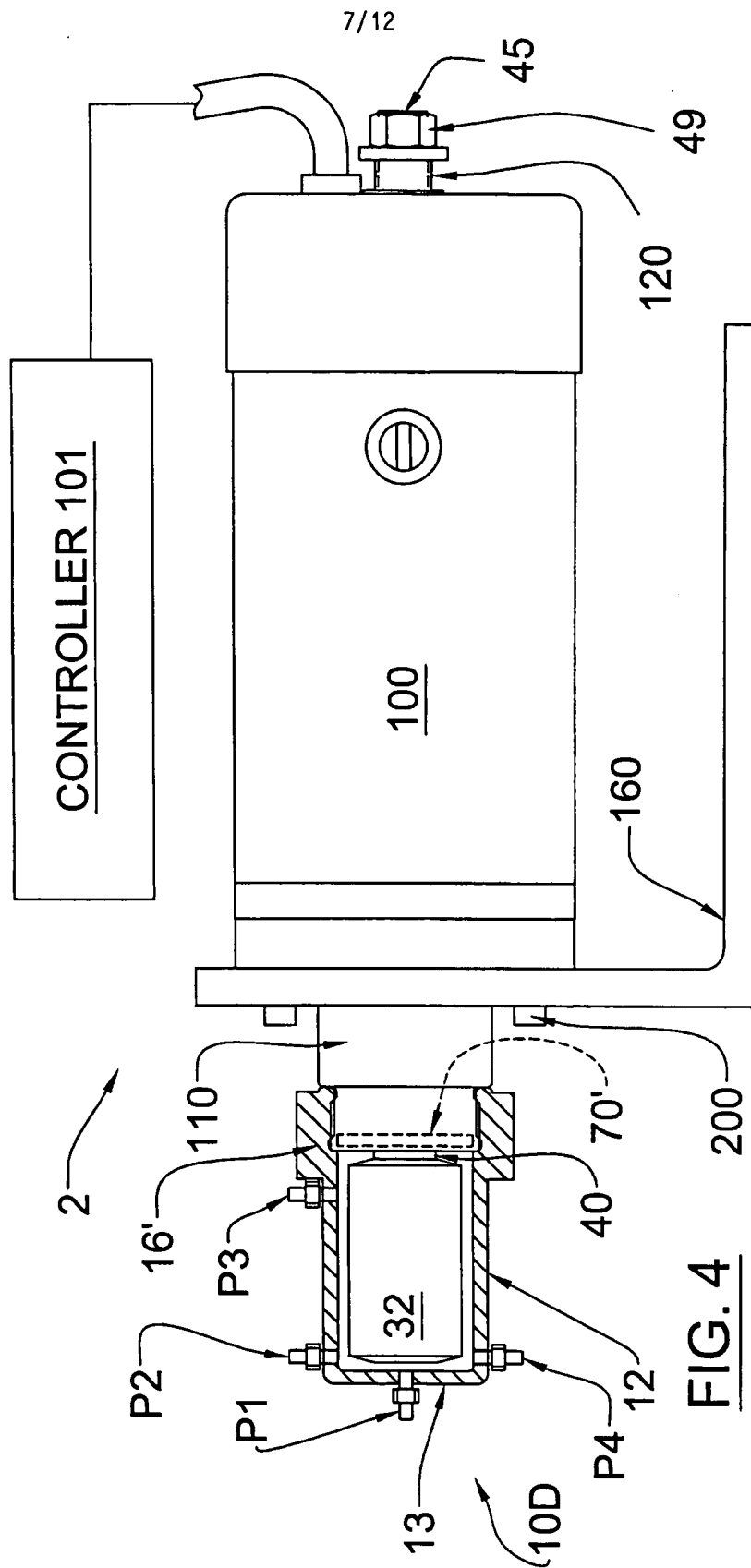


FIG. 3B

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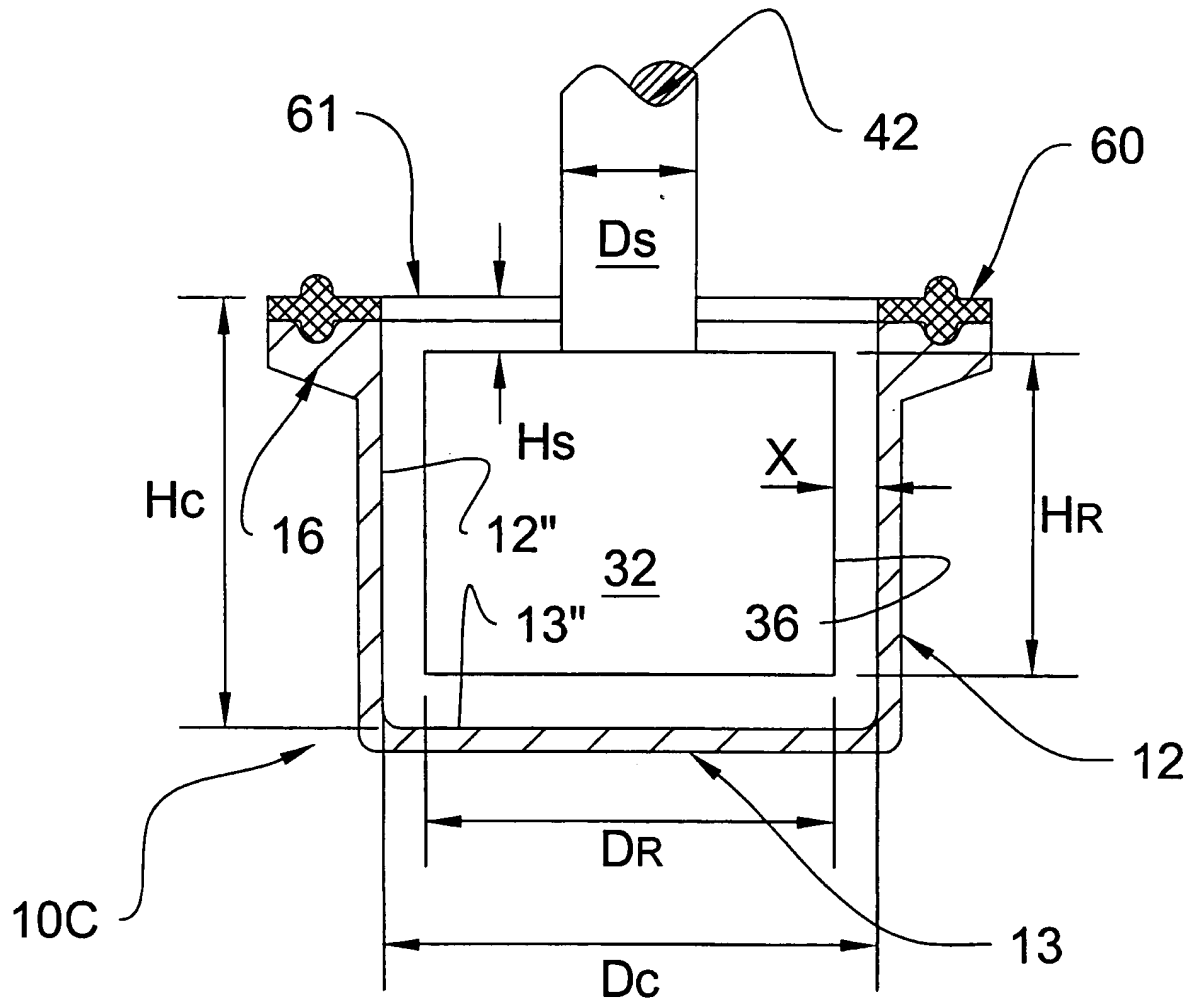


FIG. 5

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FIG. 6

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FIG. 7

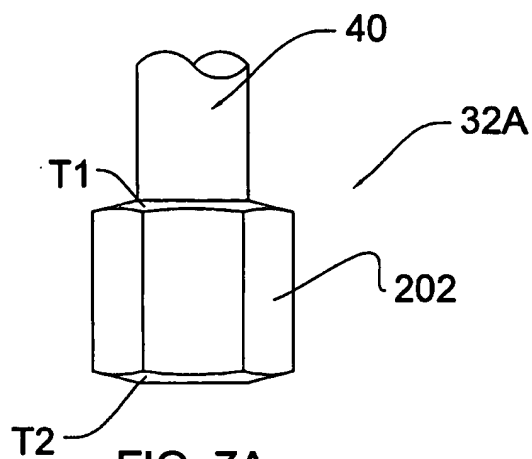


FIG. 7A

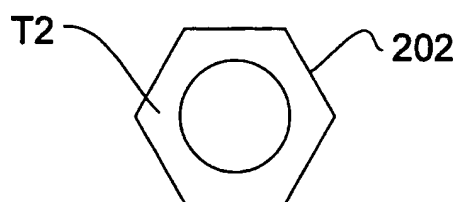


FIG. 8

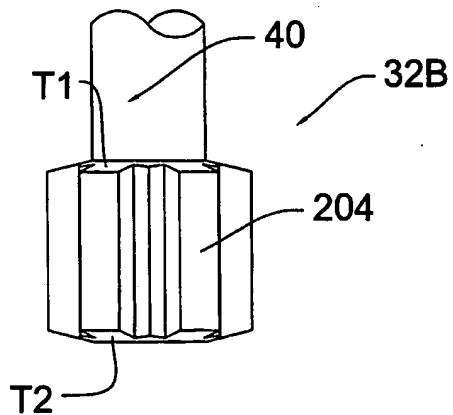


FIG. 8A

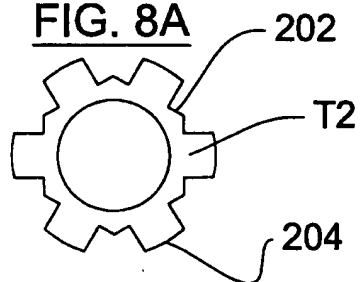


FIG. 9

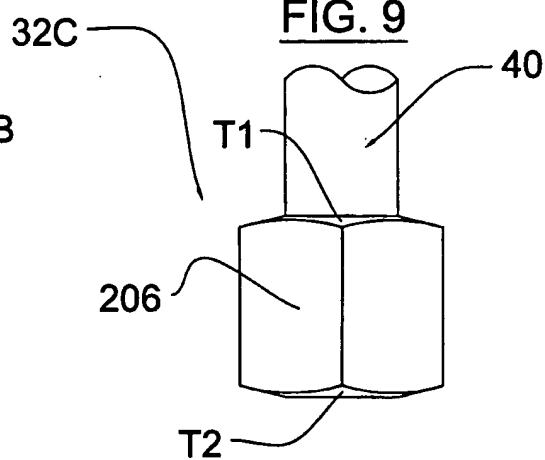
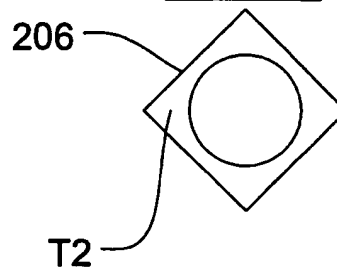


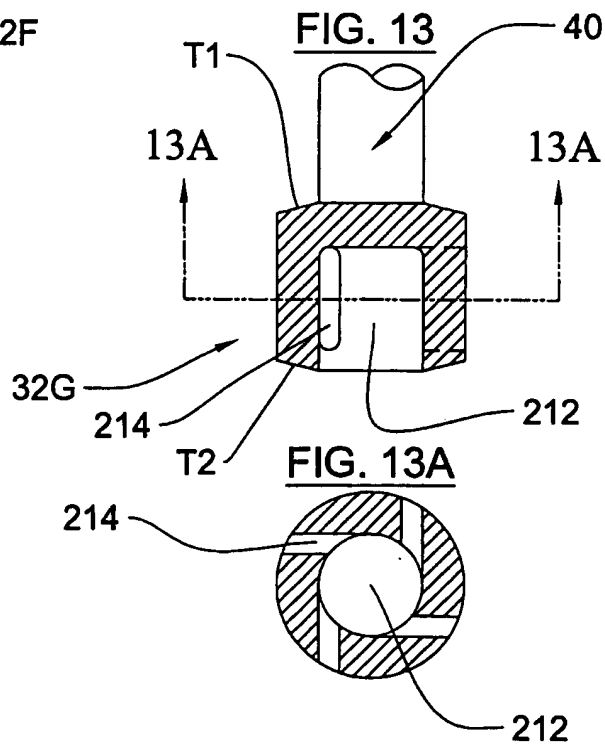
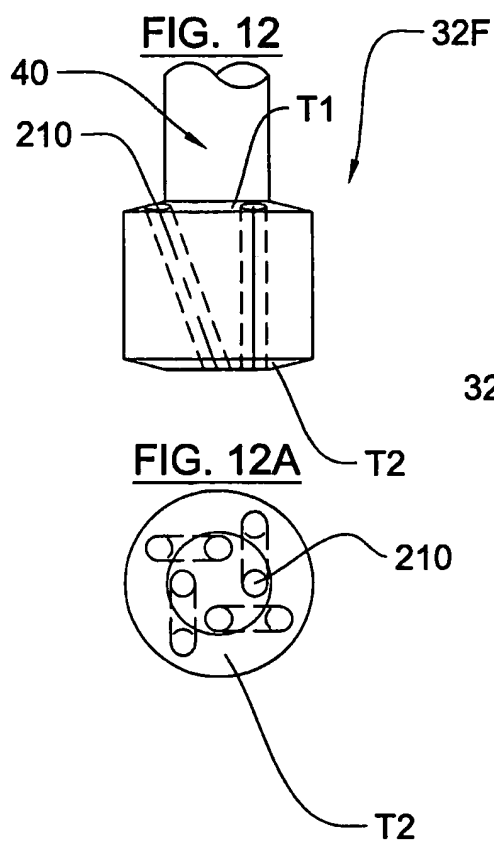
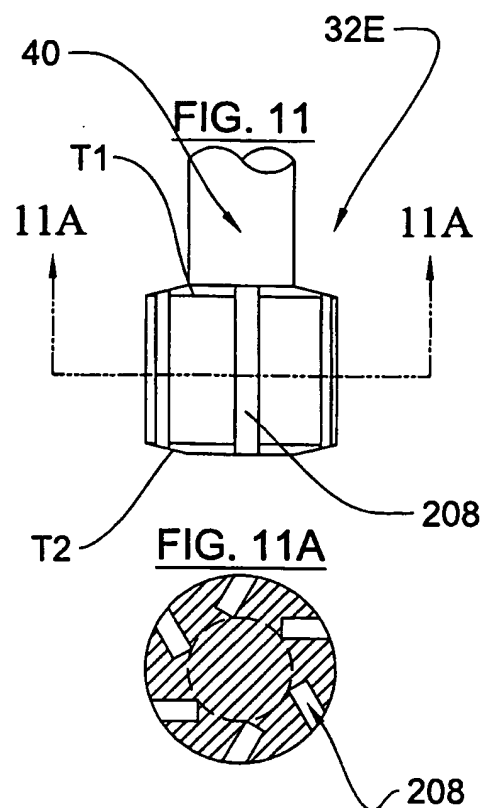
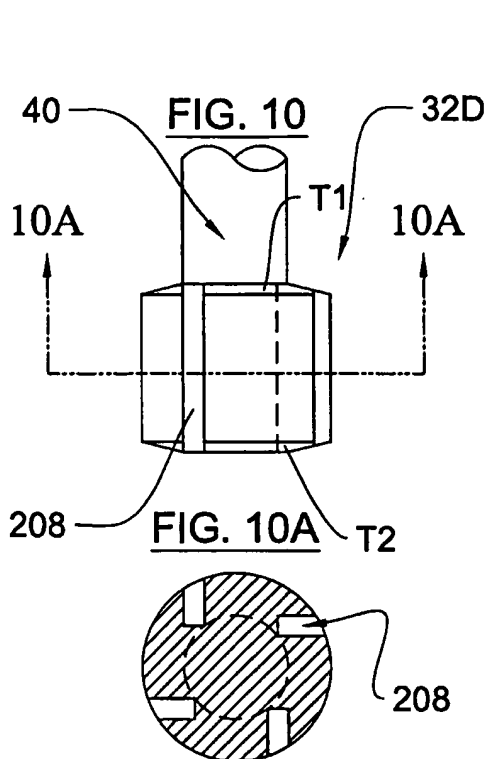
FIG. 9A



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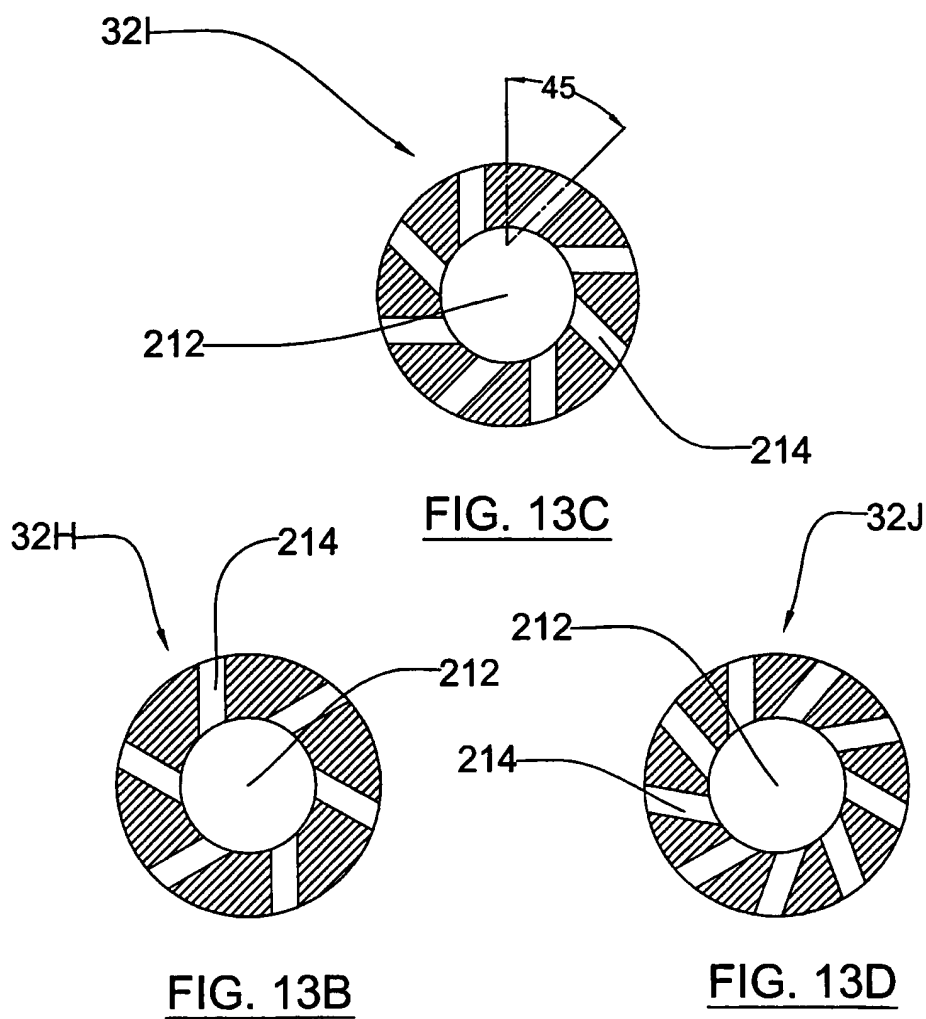
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INTERNATIONAL SEARCH REPORT

Int. National Application No

PCT/US 00/14705

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B02C17/16 B02C17/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 B02C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | EP 0 483 808 A (MATSUSHITA ELECTRIC IND CO LTD) 6 May 1992 (1992-05-06) the whole document --- | 1,23,28, 31,34 |
| A | US 5 464 163 A (ZOX HENNING) 7 November 1995 (1995-11-07) claims 1,7,14 --- | 1,23,28, 31,34 |
| A | US 5 183 215 A (GETZMANN HERMANN) 2 February 1993 (1993-02-02) column 4, line 44 -column 5, line 68; figure 1 --- | 1,23,28, 31,34 |
| A | EP 0 686 428 A (EASTMAN KODAK CO) 13 December 1995 (1995-12-13) cited in the application the whole document --- | 1,23,28, 31,34 |
| -/-- | | |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

20 September 2000

Date of mailing of the international search report

27/09/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 eponl,
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Verdonck, J

INTERNATIONAL SEARCH REPORT

Int .tional Application No
PCT/US 00/14705

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------------|
| A | US 5 718 388 A (CZEKAI DAVID A ET AL) 17 February 1998 (1998-02-17) cited in the application abstract ----- | 1,23,28, 31,34, 37-46 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/14705

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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